REMARKS

Upon entry of this amendment Claims 8-20 will be pending in this application.

Requirement for Restriction

Applicant acknowledges the Examiner's having made the Requirement for Restriction final. However, Applicant objects to the Examiner's characterization of the term "relative potency" as vague and indefinite and not defined in the disclosure. Applicant has provided extensive teachings on the evaluation of the antigenicity and potency of rHBsAg. See, for example, pages 11-16, Examples 2, 3, 4 and 6 and Figures 1, 2, 5 and 6 of the specification as filed.

Formal Drawings

Applicant concurrently submits Formal Drawings via First Class Mail. The set of drawings is the same as that submitted to the PCT. Applicant believes the drawings address all of the Examiner's concerns. The "A, B and C" in FIG. 6 are explained in Example 3.

Double Patenting

Applicant acknowledges the provisional rejection of the pending claims in view of copending Application No. 09/869007. Because no claims have in fact been patented, this is a provisional response. Should either application receive an indication of allowance Applicant will address this rejection as appropriate at that time.

Amendment of the Specification

The specification is amended at page 2 to complete the citation of Wampler 1985. The amendment is supported at page 9, lines 13-14.

The specification is amended at page three to insert the SEQ ID NO identifiers requested by the Examiner for FIG 3.

Amendment of the Claims

To clarify Applicant's claimed methods Claim 8 is amended to recite that the HBsAg provided in step a is "soluble". The amendment is supported at pages 7-8 and Example 1. Claim 8 is amended to recite that the "the antigenicity of the rHBsAg produced after step d is

greater than the antigenicity of the rHBsAg provided in step a." Support for the amendment is found throughout the specification.

Amendments for antecedent basis, grammatical and typographic corrections are discussed further below.

No issue of New Matter is believed to be raised by the present amendments.

Rejections under 35 USC § 112, second paragraph

The Examiner rejected Claim 8 over the recitation of "about", alleged that the claim does not relate the result to the preamble, and found the wording of the temperature adjustment in step c to be unclear.

Claim 8 is amended to relate the preamble and the final clause of the claim.

Applicant believes that the Examiner has misunderstood the nature of step c of Claim 8. Apparently, Applicant's use of the word "from" to denote the range of "from about 34°C to about 38°C" was, instead, read by the Examiner to indicate that the temperature should be about 34°C to start and is then adjusted to about 38°C. The word "from" has been deleted from step c. The temperature of the step is performed at a temperature within the range of "about 34°C to about 38°C". There is no limitation in the claim that the rHBsAg be at any particular temperature before the temperature is adjusted per step c.

The term "about" is discussed in the last paragraph of page six of the specification.

Claim 9 was rejected over the an alleged requirement of a starting temperature. Like Claim 8, there is also no limitation of a particular temperature before the step recited in Claim 9 can be carried out.

Claim 10 was rejected over the recitation of "about" and "corresponding disulfide compounds". Regarding "about", the Examiner is respectfully directed to the last paragraph of page six of the specification. Regarding the recitation of "corresponding disulfide compounds", the Examiner is directed to the paragraph bridging pages two and three of the specification as well as the first full paragraph on page three.

Claims 12-14, 16, 18 and 20 were rejected over the recitation of "about". The Examiner is respectfully directed to the last paragraph of page six of the specification.

Claim 14 was rejected for insufficient antecedent basis for the term "glutathione to oxidized glutathione". The Claim is amended to recite "thiol to disulfide". Antecedent for the amendment is found in the Claims 10 and 11.

Claim 18 was rejected over the temperature issue raised above. Applicant relies on the discussion above.

Claim 19 was rejected as repeating the steps of Claim 17. Claim 19 is amended to correct a typographical error by amending the claim to depend from Claim 18.

Claim 20 was rejected for insufficient antecedent basis for step d. Applicant notes that step d appears in Claim 8, from which Claim 20 ultimately depends.

In view of Applicant's amendments and remarks, Applicant respectfully requests that the rejections stated against claims be withdrawn.

Rejections under 35 USC § 103

Claims 8-16 and 20 were rejected in view of Builder *et al.*, US 4,620,948. Applicant respectfully traverses.

The Examiner stated that one of skill in the art "would have been motivated to use the method of Builder et al. to ensure proper protein folding and increase the yield obtained by **eliminating refractile bodies** (cite omitted). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Builder et al. teaches HbsAg is conventionally produced by cell culture (cite omitted) which results in **insoluble refractile bodies** and the reference teaches a method of **freeing recombinant proteins from refractile bodies**." (Action at page 5, lines 11-17; **emphasis added**)

Applicant agrees with the Examiner's interpretation of the teachings of Builder *et al.*, that one would be motivated to employ the Builder method to eliminate refractile bodies and that one would reasonably expect to successfully employ that method to free recombinant HBsAg from insoluble refractile bodies. However, Applicant is not claiming methods for eliminating refractile bodies, eliminating insoluble refractile bodies or freeing recombinant HBsAg from refractile bodies. In fact, Applicant teaches that the method is employed on soluble HBsAg. (Specification at pages 7-8 and Example 1).

To clarify Applicant's claimed methods Claim 8 is amended to recite that the HBsAg provided in step a is "soluble".

Because the teachings of Builder *et al.*, are directed to solving problems involved with freeing recombinant protein from refractile bodies, Applicant does not see how the reference could provide motivation for one of ordinary skill in the art to produce the present invention. In fact, because the HBsAg is already soluble at the beginning of the present method,

Applicant believes that one of ordinary skill in the art would see the method of Builder *et al.*, as serving no relevant purpose – there are no refractile bodies to eliminate. Therefore, one of ordinary skill in the art would not look to Builder *et al.*

Without motivating one of ordinary skill in the art, the reference cannot form the basis for a *prima facie* case of obviousness against the present claims. Therefore, Applicant respectfully requests that the stated rejection of Claims 8-16 & 20 be withdrawn.

Claims 17 – 19 were rejected over Builder *et al.*, in view of Petre *et al.*, or Even-Chen. Because neither Petre *et al.*, or Even-Chen make up for the deficiency of Builder *et al.*, as the primary reference, the combinations can not provide the basis for a *prima facie* case of obviousness of the present claims. Therefore, Applicant respectfully requests that the stated rejections against Claims 17-19 be withdrawn.

CONDITIONAL PETITION

Applicant hereby makes a Conditional Petition for any relief available to correct any defect in connection with this filing, or any defect remaining in this application after this filing. The Commissioner is authorized to charge deposit account 13-2755 for the petition fee and any other fee(s) required to effect this Conditional Petition.

CONCLUSION

Claims 8-20 are now believed to be presented in condition for Allowance. An early indication of the same is requested. The Examiner is invited to contact Applicant's Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

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Date: October 10, 2002

VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

8. (AMENDED) A method of [making] increasing the antigenicity of recombinant hepatitis B surface antigen (rHBsAg) comprising:

a) providing soluble sterile filtered rHBsAg purified from a cell culture,

b) adding a redox buffer to the rHBsAg,

c) adjusting the temperature to [from] about 34°C to about 38°C,

d) incubating the rHBsAg at about 34°C to about 38°C for about 40 to about 240 hours[.],

wherein the antigenicity of the rHBsAg produced after step d is greater than the antigenicity of the rHBsAg provided in step a.

14. (AMENDED) The method according to Claim 13 wherein the ratio of [glutathione] thiol to [oxidized glutathione] disulfide is selected from the group consisting of about 20:1, about 10:1, about 10:4, about 5:1, about 2:1 and about 1:1.

19. (AMENDED) The method according to Claim [17] 18 further comprising the steps of

g) adding an aluminum adjuvant, and

h) co-precipitating the rHBsAg and the adjuvant.